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10/590,446	10/10/2007	Gabor Forgacs	UMO 1561.1	8467

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EXAMINER	
SRIVASTAVA, KAILASH C	

ART UNIT	PAPER NUMBER
1653	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspatents@senniger.com

Office Action Summary	Application No.	Applicant(s)
	10/590,446	FORGACS ET AL.
	Examiner	Art Unit
	KAILASH C. SRIVASTAVA, Examiner	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-17 and 52-66* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

1. The amendment, response and remarks filed 06 June 2011 to the Office Action with Non-Final Rejection mailed 06 January 2011 is acknowledged and entered.

Claims Status

2. According to the amendment filed 06 June 2011, following is the current status of the Claims in the instant application:

- Claims 10, 18-51 and 67-84 have been cancelled;
- Claims 1-9 and 11-17 have been withdrawn;
- Claims 1 and 52-66 have currently been amended; and
- Claims 52-66 are examined on merits.

Withdrawls

3. Considering the amendment and response filed 06 June 2011, the following objections and rejections in the Office Action with Non-Final Rejection mailed 06 January 2011 are hereby withdrawn:

- Objection to Claims 53-63 and 66 for lack of a "," before the word, "wherein" at line 1 of said Claims;
- Anticipatory rejection of Claims 52-53, 56, 58 and 62-63 under 35 U.S.C. §102(b) by Furukawa et al (2001.Tissue-engineered skin using aggregates of normal human skin fibroblasts and biodegradable material. J Artif. Organs, Volume 4, Pages 353-356);
- Obviousness rejection of Claims 52-53 and 56-66 under 35 U.S.C. §103 (a) over combined teachings from Furukawa et al. (2001.Tissue-engineered skin using aggregates of normal human skin fibroblasts and biodegradable material J Artif.

Organs, Volume 4, Pages 353-356) in view of Boland et al. (US 2004/0237822 A1) and Roth et al. (2004. Inkjet printing for high-throughput cell patterning. Biomaterials, Volume 25, Pages 3707–3715); and

- Obviousness rejection of Claims 54-55 under 35 U.S.C. § 103 (a) over combined teachings from Furukawa et al (2001.Tissue-engineered skin using aggregates of normal human skin fibroblasts and biodegradable material J Artif. Organs, Volume 4, Pages 353-356) in view of Boland et al., (US 2004/0237822 A1) and Roth et al. (2004. Inkjet printing for high-throughput cell patterning. Biomaterials, Volume 25, Pages 3707–3715) as applied to Claims 52-53 and 56-63 above and further in view of Mizumoto et al (1999. Formation of cylindrical multicellular aggregate (cylindroid) and expression of liver specific functions of primary rat hepatocytes. Cytotechnology, Volume 31, Pages 69–75).

Informals

4. The instant non-provisional application (i.e., 10/590,446) currently under prosecution at the United States Patent and Trademark Office (i.e., USPTO) is now assigned in **Art Unit 1653 to** Examiner Kailash C. Srivastava. To expedite the prosecution of the instant application (i.e., 10/590,446) and in correlating any papers for the instant application (i.e., 10/590,446), please ensure that all further correspondence regarding the instant application (i.e., 10/590,446) is directed to Examiner Kailash C. Srivastava in **Art Unit 1653**.

Restriction/Election

5. Applicants continue to argue regarding the improprietary of the following Restriction requirement in the Office Action mailed 09 August 2010

> "This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1and 37 C.F.R. §1.475.

In accordance with PCT rules cited *supra*, applicant is required, in reply to the instant Office Action, to select a single invention to which the claims must be restricted.

- Group I, consisting of claims 1, 5-9, and 11-17 drawn to a method to produce a plurality of fused cell aggregates forming a three-dimensional structure, wherein a layer of matrix is deposited on a substrate; at least one aggregate of plurality of cells is embedded in said layer and at least one aggregate of cells fuses with at least one other aggregate of plurality of cells;

- Group II consisting of Claims 2-4 drawn to another method, wherein the matrix layer constitutes a first layer, the plurality of cell aggregates constitutes a first plurality of cell aggregates and predetermined pattern constitutes a first pattern, said method further comprises depositing a second layer of the matrix on the first layer and embedding a second plurality of cell aggregates in the second layer to form a second predetermined pattern and further allowing at least one aggregate of cells in the first layer to fuse with at least one aggregate of plurality of cells in the second layer; and

- Group III, consisting of claims 52-66, drawn to a three dimensional layered structure comprising at least one layer of a biocompatible matrix and a plurality of cell aggregates, each cell aggregate comprising a plurality of living cells, wherein cell aggregates are embedded in the at least one layer of biocompatible matrix in a pre-determined pattern.

In addition to the requirement that a Group of inventions must belong to one of the specific categories provided by PCT Rule 13.2, the inventions in the category, e.g., as a composition and a method of use of said composition, must have a special technical feature that unites them. See Patent rules under 37 C.F.R. §1.475, where a special technical feature is a contribution OVER THE PRIOR ART."

Applicants' alleged special technical feature is "cell aggregates are embedded according to a predetermined, non-random pattern, wherein the cell aggregates have predetermined positions in the pattern' (See, Remarks filed 06 June 2011, Page 6, Lines 13-15).

Said alleged technical feature is taught by Tang et al. (see below).

For additional details on "special technical feature" and the invention, Examiner, respectfully refers Applicants' attention to M.P.E.P. Appendix AI, Annex B.

Claim Rejections - 35 USC §102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> ***A person shall be entitled to a patent unless –***
>
> > ***(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.***

7. Amended Claims 52-53, 56, 58 and 61-63 are rejected under 35 U.S.C. §102(b) as anticipated by Tang et al (2003. Molding of Three-Dimensional Microstructures of Gels. Journal of American Chemical Society (i.e., J. AM. CHEM. SOC.), Volume 125, Number 43, Pages 12988-12989).

Amended Claims 52-53, 56, 58 and 61-63 claim a three dimensional layered structure comprising:

- at least one layer of a biocompatible matrix (Claim 52);
- a plurality of uniformly shaped and sized (Claim 53) spherical (Claim 56) cell aggregates, each comprising a plurality of living cells (Claim 52) of a single type (Claim 58);

- said cell aggregates are embedded in a non-random predetermined pattern in at least one layer of said biocompatible matrix (Claim 52);

- at least one layer of matrix is 100 micron to 600 micron thick biocompatible layer (Claim 61);

- said biocompatible matrix is selected from the group consisting of: gels that are thermo-reversible, photosensitive, pH sensitive, cell specific or combinations thereof (Claim 62);

- at least one layer of a biocompatible matrix comprises at least two different types of biocompatible matrices (Claim 63).

The three dimensional layered structure claimed in instantly presented Claims 52-53, 56, 58 and 61-63 is interpreted to be a composition comprised of different components.

Regarding limitations in Claims 52-53, Tang et al., teach three dimensional, at least bi-layered microstructures comprised of hydrogels (Page 12988, Column 1, Lines 9-11; Figure 1), wherein cell arrangement can be controlled to comprise patterned arrays of distinct cell populations in stacked cell layers (Page 12988, Column 2, Lines 2-6 under Figure 1; Figure 2) and at least one layer is comprised of cells embedded in a biocompatible matrix (i.e., collagen; Page 12988, Column 2, Lines 23-25 under Figure 1). Said layer is comprised of a plurality of cell aggregates, each comprised of a plurality of cells that are randomly displaced in a predetermined cell aggregate patterns (Figure 2A), wherein cell aggregates are substantially of uniform size and shape because most of the aggregates are spherical (limitation in Claim 53).

Regarding limitations in amended Claim 56, Tang et al., teach that most of the aggregates are substantially spherical (Figure 2A).

For limitation in Claim 58, Tang et al., teach said cell are of single type (i.e., human fibroblasts; Page 12988, Column 2, Lines 8-11 under Figure 1).

Tang et al., further teach limitation in amended Claim 61 because the hydrogel/collagen (i.e., biocompatible matrix) layer is at least 100 μm thick (Legend to Figure 2, Lines 4 and 9); limitation in Claim 62 because collagen is inherently pH sensitive and the limitation in amended Claim 63 because the top layer is comprised of a gelled collages suspension embedded with cells against poly- dimethylsiloxane (i.e., PDMS) stamp (Page 12989, Column 1, Lines 3-5 under Figure 2).

Thus, as illustrated in the discussion *supra*, Tang et al., teach each and every limitation presented in instantly recited amended Claims 52-53, 56, 58 and 61-63.

Therefore, the reference is deemed to anticipate the instantly recited amended Claims 52-53, 56, 58 and 61-63.

Claim Rejections - 35 U.S.C. §103

8. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

9. Claims 52-53 and 56-66 are rejected under 35 U.S.C. §103 (a) as obvious over combined teachings Tang et al (2003. Molding of Three-Dimensional Microstructures of Gels. Journal of American Chemical **Society (i.e., J. AM. CHEM. SOC.), Volume 125, Number 43, Pages 12988-12989**), in view of Boland et al. (US 2004/0237822 A1).

Claims 52-53 and 56-63 claim a three dimensional layered structure comprising:

- at least one layer of a biocompatible matrix (Claim 52);
- a plurality of uniformly shaped and sized (Claim 53) spherical (Claim 56) cell aggregates, each comprising a plurality of living cells (Claim 52) of a single type (Claim 58);

- said cell aggregates are embedded in a non-random predetermined pattern in at least one layer of said biocompatible matrix (Claim 52);
- said cell aggregates are about100μm to about 600μm in diameter (Claim 57);
- each of said aggregate comprises plurality of living cells of two different types designated as of first type and second type as claimed in Claim 59;
- plurality of said aggregates comprise plurality of living cells of two different types designated as of first type and second type as claimed in Claim 60;
- said biocompatible matrix is about100μm to about 600μm thick (Claim 61);
- said biocompatible matrix is selected from the group consisting of: gels that are thermo-reversible, photosensitive, pH sensitive, cell specific or combinations thereof (Claim 62);
- at least one layer of a biocompatible matrix comprises at least two different types of biocompatible matrices (Claim 63);
- said biocompatible matrix is present as two separate layers and cell aggregates are embedded in each of the two biocompatible matrix layers (Claim 64);
- said biocompatible matrix in Claim 64 is present at least as one additional layer and cell aggregates are embedded in said at least one additional layer (Claim 65); and
- said biocompatible matrix present in first layer is of a different type than that in the second layer (Claim 66).

The three dimensional layered structure claimed in instantly presented Claims 52-53, 56, 58 and 62-66 is interpreted to be a composition comprised of different components.

Regarding Claims 52-53 and 56-66, Tang et al's teachings have been discussed *supra.* Tang et al., however, are silent regarding diameter of said aggregates (i.e., limitation of Claim 57) and each of said aggregates or plurality of aggregates comprising plurality of living cells of two different types (i.e., limitations in Claims 59-60) .

Boland et al., teach:

- an array of viable cells on a gel (Page 1, Column 2, Paragraph (i.e., ¶) 0008, Lines 2-4 and Claim 54) in form of cell aggregates, the aggregates may be formed on a variety of substrates including scaffolds (Page 4, Column 2, ¶0049, Lines 3-5) and/or gels, wherein gels are of collagen, or polyglycolic acid (Page 5, Column 2, continuation of ¶ 0052, Lines 1-4 and Claims 56 and 65);

- said cell aggregates having a diameter in range of about 100 μm to 3 millimeters (Page 4, Column 2, ¶ 0047, Lines 6-7);

- said cell aggregates are made of a single cell type or multiple cell types (Page 4, Column 2, ¶ 0047, Lines 1-5; Claim 63);

- the thickness of cell and/or matrix layers range from 2 μm to 3 mm (Page 7, Column 1, ¶ 0061, Lines 1-13);

- the three dimensional structure comprised of cell aggregates comprises alternating layers of cell aggregates and the matrix material , wherein said layers are 2 to multiple layers (Page 5, Column 1, continuation of ¶ 0050, Lines 1-4; Figure 7; Page 7, Column 1, continuation of ¶ 0060, Lines 7-18);
- the limitations in Claims 64-65 that said biocompatible matrix is present as a separate layer beneath cell aggregates or above the cell aggregates or between the cell aggregate layers (Page 5, Column 1, continuation of ¶ 0050, Lines 1-4).

Thus, as discussed *supra,* Boland et al., teach a composition comprising a three dimensional layered structure/composition comprising an array of viable cells in form of

aggregates\ that can be formed on a variety of materials including gels and scaffolds which is the limitation in instantly presented Claim 52. Please note an array is a non-random predetermined pattern. Boland et al., teach the limitation in instantly presented Claim 57, because Boland et al., further teach that the diameter of said aggregates varies in the range of about 100 μm to 3 mm which range encompasses the diameter of about100 μm to about 600 μm; and the limitation in instantly presented Claims 59-60 because said aggregates/arrays are made of single or multiple types of cells. Boland et al., also teach the limitation in instantly presented Claim 61 because the thickness of each of the matrix and/or cell aggregate layer ranges from 2 μm to 3 mm, which range encompasses the thickness of about100 μm to about 600 μm. Boland et al., also teach the limitations in Claims 64-65 because at Page 5, Boland et al. further teach that said biocompatible matrix is present as a separate layer beneath cell aggregates or above the cell aggregates or between the cell aggregate layers. Since the biocompatible matrix layers are made of matrices comprised of e.g., collagen or agarose or glycolic acid or any polymer thereof, Boland et al. also teach the limitation in Claim 66 that the biocompatible matrix in one layer comprises a biocompatible matrix different than the one in the other layer.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Tang et al., according to those from Boland et al. to obtain a three dimensional layered structure comprised of living cell aggregates embedded in a biocompatible matrix in a non-random predetermined pattern**; because Boland et al.** teach a composition comprising a three dimensional layered structure/composition comprising an array of viable cells in form of aggregates that can be formed on a variety of materials including gels. Boland et al., further teach said aggregates/arrays are made of single or multiple types of cells and further teach that said biocompatible matrix is present as a separate layer beneath cell aggregates or above the cell aggregates or between the cell aggregate layers. Additionally, since the biocompatible matrix layers are made of matrices comprised of e.g., collagen, agarose, glycolic acid, or any polymer thereof, Boland et al., also teach that the biocompatible matrix in one layer comprises a biocompatible matrix different than the one in the other layer.

From the teachings of the references cited supra, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claims 54-55 are rejected under 35 U.S.C. § 103 (a) as obvious over combined teachings from Tang et al (2003. Molding of Three-Dimensional Microstructures of Gels. Journal of American Chemical Society (i.e., J. AM. CHEM. SOC.), Volume 125, Number 43, Pages 12988-12989). in view of Boland et al., (US 2004/0237822 A1) as applied to Claims 52-53 and 56-63 above and further in view of Mizumoto et al (1999. Formation of cylindrical multicellular aggregate (cylindroid) and expression of liver specific functions of primary rat hepatocytes. Cytotechnology, Volume 31, Pages 69–75).

Amended Claim 54 recites an additional limitation that cell aggregates are cylindrical and amended Claim 55 recites that said cylindrical aggregates are 100 micron to 600 micron in cross sectional diameter.

The three dimensional layered structure claimed in instantly presented Claims 54-55 is interpreted to be a composition comprised of different components.

Mizumoto et al., teach cylindrical multicellular aggregate (i.e., cylindroid) of primary rat hepatocytes and further teach that said cylindroids are approximately 200 μm to 500 μm in diameter and 500 μm to 2 mm in length (abstract, Lines 1-5). Please note that the diameter of a cylinder is always in a cross section of said cylinder.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made and one having ordinary skill in the art at the time of the claimed invention would have been motivated to modify/combine the teachings from Tang et al., according to those from Boland et al., and Mizumoto et al., to obtain a three dimensional layered structure comprised of living cell aggregates embedded in a biocompatible matrix in a non-random predetermined pattern, wherein said aggregates are spherical and cylindroids**, because Boland**

et al. teach a composition comprising a three dimensional layered structure/composition comprising an array of viable cells in form of aggregates\ that can be formed on a variety of materials including gels and scaffolds. Boland et al., additionally teach that said biocompatible matrix is present as a separate layer beneath cell aggregates or above the cell aggregates or between the cell aggregate layers. Additionally, since the biocompatible matrix layers are made of matrices comprised of e.g., collagen, agarose, glycolic acid, or any polymer thereof; Boland et al., also teach that the biocompatible matrix in one layer comprises a biocompatible matrix different than the one in the other layer and Mizumoto et al., teach cylindrical multicellular aggregate (i.e., cylindroid), said cylindroids are approximately 200 μm to 500 μm in diameter and 500 μm to 2 mm in length.

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

11. For the aforementioned reasons, no claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:00 A.M. to 5:30 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue X. Liu can be reached at (571)-272-5539 Monday through Friday 9:00 A.M. to 4:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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